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PHASE 3 SUMMARY OF MRID 00116596 AND RELATED MRID 00149530:

TERATOLOGY STUDY IN RABBITS

STUDY # 281014

FLUMETRALIN

GUIDELINE REFERENCE:

83-3(B) TERATOGENICITY - RABBIT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

5 OCTOBER 1990

ORIGINAL STUDY PREPARED BY:

SCIENCE APPLICATIONS, INC.

LA JOLLA, CALIFORNIA

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

GOOD LABORATORY PRACTICE STATEMENT

Science Applications, Inc. is no longer conducting toxicology business. Therefore, a GLP statement cannot be obtained from a study director or laboratory management. The attached pages from the report on this study indicate that the study was conducted under FDA Good Laboratory Practice Regulations (21 CFR 58).

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR Part 160 (see above).

Submitter/Sponsor of Study:

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

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QUALITY ASSURANCE STUDY INSPECTION AND COMPLIANCE STATEMENT

STUDY TITLE: A Teratology Study of CGA-41065 Technical in New Zealand White Rabbits

TESTING FACILITY:

Science Applications, Inc.
Division of Toxicology
476 Prospect Street
P.O. Box 1454
La Jolla, CA 92038

SPONSOR NAME AND ADDRESS:

Ciba-Geigy Corporation
Agricultural Division
410 Swing Road
P.O. Box 11422
Greensboro, NC 27409

SPONSOR-STUDY NUMBER:

281014

PRINCIPAL INVESTIGATOR:

Stephen B. Harris, M.S.

QUALITY ASSURANCE STATEMENT:

The following statements address the Food and Drug Administration's Good Laboratory Practices (GLP) requirements (CFR Title 21, Chapter I, Part 58 Subpart B, Section 58.35(b)(7)) for final reports.

A. Inspection and Reporting Statement: This study was inspected according to the Quality Assurance Unit's Standard Operating Procedures on the following dates:

Dates of Inspection	Phase of Study	Date Inspection Findings Reported to Principal Invest.	Dates of Management Reports
August 18, 1981	Animal Receipt	August 20, 1981	August 31, 1981
September 9, 1981	Animal Identification, Randomization-Breeding, PLH Administration	September 10, 1981	October 27, 1981
September 10, 1981	Test Article Formulation	September 10, 1981	October 27, 1981
September 14, 1981	Dose Administration	September 14, 1981	October 27, 1981
September 17, 1981	AM Clinical Observations	September 17, 1981	October 27,1981
September 22, 1991	Protocol Compliance Review	September 22, 1981	October 27, 1981
September 23, 1981	PM Clinical Observations	September 23, 1981	October 27, 1981
October 12, 1981	Cesarean Section	October 13, 1981	October 27, 1981
October 19, 1981	Visceral Examination	October 19, 1981	October 27, 1981
November 30, 1981	Skeletal Examinations	November 30, 1981	February 2, 1981
April 7, 1982	Raw Data Review	Not Reported	--
April 27, 1982	Draft Final Report Review	April 27, 1982	--

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B. Compliance Statement:

The study was conducted in compliance with Good Laboratory Practices regulations.

SKKeener

August 23, 1982

Sharon K. Keener
Quality Assurance Inspector and Manager

Date

CGA/SAI 281014

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Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

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83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y — Technical form of the active ingredient tested.
2. Y — At least 20 pregnant animals/dose group for mice, rats or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3. Y — At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.* Y — At the low dose, no developmental toxicity is reported.
5. Y — Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.* Y/N — Analysis for test material stability, homogeneity and concentration in dosing medium
7. Y — Individual daily observations.
8. Y — Individual body weights.
9. N — Individual food consumption.
10. Y — Necropsy on all animals
11. Y — Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. Y — All ovaries examined to determine number of corpora lutea.
13. Y — Individual litter weights and/or individual fetal weights per sex/litter.
14. Y — Individual fetus external examination.
15. Y — Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. Y — Individual fetus soft tissue examination.

Criteria marked with a * are supplemental and may not be required for every study.

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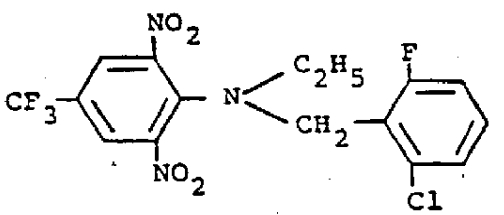
IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name:	N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine
	or
	2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine
Common Name:	Flumetralin
Trade Name:	Prime +®
CIBA-GEIGY Code Number:	CGA-41065
CAS Registry Number:	62924-70-3
EPA Shaughnessy Number:	Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

PM3006899792

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Flumetralin: 83-3(B): Teratology Study in the Rabbit

1. The test article was Flumetralin (CGA-41065) Technical, a bright orange crystalline substance, FL-810824, purity 92.7%.

2. There were 16 female New Zealand white rabbits in each of three test groups, 15 in the high-dose group, and 16 in the concurrent control group. The dose levels were 0 (control), 3, 10, 30, and 60 mg/kg of body weight per day of dosing.

3. There were 11, 10, 12, 11, and 10 viable litters in the control, 3, 10, 30, and 60 mg/kg/day groups, respectively. Of 14 pregnant does in the control group, one was removed from the study (apparent enteritis) and two had no live or dead fetuses. Of 14 pregnant does in the 3 mg/kg/day group, two delivered prematurely and two had no live or dead fetuses. Of 14 pregnant does in the 10 mg/kg/day group, two had no live or dead fetuses. Of 12 pregnant does in the 30 mg/kg/day group, one had no live or dead fetuses. Of 12 pregnant does in the 60 mg/kg/day group, one aborted and one had no live or dead fetuses.

4. One abortion occurred in the high-dose group, verifying findings in the range-finding study.

5. The developmental no-observable-effect level in this study was 60 mg/kg/day, the highest dose tested.

6. The animals were dosed by gavage for 13 consecutive days, from Day 6 through Day 18 of gestation (beginning September 11, 1981).

7. Test article/vehicle suspensions were prepared every three days. A sample from the first and last preparations of each dose level was retained and analyzed for concentration approximately two months after the preparations were mixed. Analytical concentrations averaged 113% and 112% of target concentrations for first and last sets of dosing suspensions, respectively. The dosing suspensions were not analyzed for homogeneity or stability.

8. Does were observed daily for physical signs and/or general appearance. No treatment-related observations were noted. Incidental observations included anorexia in all five groups, nasal or ocular discharge, discharge in pan, mass on jaw or neck, diarrhea, and dyspnea.

9. Body weights were recorded during acclimation and on Days 0, 6-18, 25, and 30 of presumed gestation. There were no significant differences among the groups in absolute body weight or body weight change.

10. Food consumption was not measured in this study.

11. Does which were removed from the study, aborted, or delivered early were not included in the statistical analyses of the data. All other does were sacrificed on Day 30 of presumed gestation. The thoracic and abdominal cavities were opened and the reproductive organs were examined in situ. The uterus was excised and opened, and the location and distribution of live and dead fetuses and number and type of resorptions were recorded. No treatment-related findings were noted at necropsy.

Parameter	Dose Level (mg/kg/day) 0	3	10	30	60
Total Pregnant Does (N)	14	14	14	12	12
Removed From Study	1	0	0	0	0
Delivered Early	0	2	0	0	0
Aborted	0	0	0	0	1
On-Schedule Laparohysterectomy	13	12	14	11	10
No Fetuses (live or dead)	2	2	2	1	1
Parameters for On-Schedule Laparohysterectomy Does					
Live Fetuses (mean/litter)	5.3	5.8	5.6	5.8	6.5
Live Fetuses (percent)	100.0	93.2	98.8	98.6	98.6
Fetal Sex Ratios (% males)	56.5	50.7	54.5	48.6	54.9
Resorbed Fetuses (mean/litter)	1.1	0.8	1.1	1.2	0.6

12. Ovaries from all animals were examined to determine the number of corpora lutea. There were no differences among the groups in the number of corpora lutea, which averaged 8.1, 7.9, 6.9, 7.2, and 7.9 in the control, 3, 10, 30, and 60 mg/kg/day groups, respectively.

13. Each apparently viable fetus in each litter was weighed individually. There were no differences among the groups in mean live fetal weights per litter for either males or females.

Mean Fetal Body Weights (g)

Sex	Dose Level (mg/kg/day) 0	3	10	30	60
Males	53.3	55.3	52.0	52.4	48.9
Females	51.8	51.0	53.7	52.8	49.6

14. Each fetus was examined for gross external abnormalities. All fetuses were subjected to a fresh visceral examination. After visceral examination, the fetuses were fixed in 70% ethanol, stained with Alizarin Red S/1% KOH, then cleared and placed in glycerin for subsequent skeletal examination.

The litter was used as the unit of analysis, and no significant differences were found for any category of observations, i.e., external, visceral, or skeletal malformations or variations. The only external malformation was runt, and the only external variation was short snout in one 10 mg/kg/day fetus. The only visceral malformation and variation (small gallbladder and incomplete partitioning of the liver) were observed in one high-dose fetus. The only skeletal malformations were sternebrae 3 and 4 fused or sternebrae 4 and 5 fused. The most frequent variations were the incomplete ossification of phalanges, metacarpals, and sternebrae. With the absence of conventional signs of embryotoxicity, none of these findings are considered to be biologically significant.

15. There were no significant changes from the Acceptance Criteria in this study. Three deviations from the Acceptance Criteria are noted. Under Item 3, there were no apparent signs of toxicity in the high-dose group. However, in a range-finding study (MRID 00116595, summarized in this Phase 3 submission), doses of 800 and 1200 mg/kg resulted in abortion, premature delivery, reduced body weight gain, increased resorptions, and reduced number of live fetuses. At 400 mg/kg, the weight gain was only 78% of control, one of six pregnant does delivered early, and two others aborted. At 100 mg/kg, two of the four pregnant does aborted. There were no abortions or early deliveries in the five pregnant controls. A dose of 100 mg/kg was considered too high for the definitive study, and 60 mg/kg was selected as the high dose for the definitive study. In this study, one abortion occurred in the 60 mg/kg group, while no abortions occurred in any of the other groups. Therefore, 60 mg/kg is considered to be an appropriate high dose for this study.

Under Item 6, the dosing suspensions were not analyzed for stability or homogeneity. This deviation is considered to be insignificant because (a) stability can be inferred from the concentration analyses which were performed approximately two months after the dosing suspensions were prepared and were found to be close to target concentrations; and (b) the procedure of the lab to maintain the dosing suspension on a stir plate during dosing would ensure homogeneity. Under Item 9, food consumption was not measured. This deviation is considered to be insignificant because the dose was administered by gavage and, in addition, there were no differences in body weights or weight gains.

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